

### **DETAILED ACTION**

The examiner notes the receipt of the amendments and remarks received in the office on 1/7/2010. Claims 72-84 have been added new. Claims 2, 5-10, 42-50, 53-56, 58-61 have been cancelled. Claims 1, 3, 4, 11-41, 51, 52, 57, 62-84 are currently pending, claims 29-40, 51-52, 57 are withdrawn and claims 1, 3, 4, 11-28, 41, 62-84 are being examined on the merits herein.

### ***Response to Remarks***

The rejection of claims 1, 11, 12, 26, 27 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1-3, 30 of U.S. Patent No. (U.S. 7,149,574) ('574), rejection of claims 1, 23, 24, 70, 71 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1-3, 6, 7, 9, 10, 11, 43, 44, 59 of U.S. Patent No. (U.S. 7,363,076), rejection of claims 1, 23, 24 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1-4, 7-10, 14 and 15 of co-pending application No. 10/917,270, rejection of claims 1, 3, 4, 11-24, 27, 63-66 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1, 2, 4, 6-8, 13-16, 30-50, 55-58, 63, 71-76, 81 of co-pending application No. 10/846, 486 are withdrawn due to Applicants' arguments found to be persuasive. Applicants' arguments regarding the rejection of claims 1, 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Puskas (US 6,429,217) have been fully considered and found to be persuasive. Accordingly, the rejection is withdrawn. Applicants' arguments regarding the 112(1) rejections and the 103(a)

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rejections have been fully considered and found not to be persuasive. Applicants' amendments necessitated the modification of the 112(1), 102 and 103 rejections and the new rejections given below. The action is made final.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 26, 27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1, 6, 12, 15 and 19 of co-pending application No. 11/060,643.

Claims 1, 26, 27 of the instant application teaches a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an effective amount of at least one beta blocker to produce a

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parasympathetic/sympathetic activity ration in at least a portion of said subject's autonomic nervous system abnormality and with at least one electrode and applying electrical energy to treat conditions like inflammatory conditions, genitourinary conditions, infectious diseases gastrointestinal conditions, endocrine conditions, orthopedic inflammatory conditions, Th-2 dominant conditions, conditions that cause hypoxia, conditions that cause hypercarbia etc.

Claims 1, 6, 12, 15 and 19 of the co-pending application teach a method of treating a subject for a condition comprising electrically modulating at least a portion of said subject's autonomic nervous system to increase the parasympathetic activity/sympathetic activity ratio in a manner effective to treat said subject for said conditions chosen from neurodegenerative conditions, gastrointestinal conditions, skin conditions, Th2 dominant conditions.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the co-pending application teaches a method of treating autonomic nervous system abnormality comprising electrically modulating at least a portion of parasympathetic/sympathetic activity.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3, 70, 78 , 79, 81-84 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1, 9, 22 and 24 of co-pending application No. 10/962,190 in view of Davies et al. (The J of Intl Med Research, 1988, 16, 173-181).

The rejected claims of the instant application teaches a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an effective amount of at least one beta blocker to treat conditions like inflammatory conditions, genitourinary conditions, infectious diseases gastrointestinal conditions, endocrine conditions, orthopedic inflammatory conditions, Th-2 dominant conditions, conditions that cause hypoxia, conditions that cause hypercarbia etc. and said method further comprises determining said parasympathetic/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system. The claims also teach administering an effective amount of at least one non-beta blocking agent including an NSAID.

Claims 1, 9, 22 and 24 of the co-pending application '190 teach a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system comprising administering at least one aldosterone antagonist or an analogue thereof such as a beta blocker to treat at least one conditions such as; neurodegenerative conditions; neuroinflammatory conditions; orthopedic inflammatory conditions; pulmonary conditions; transplant-related conditions, gastrointestinal conditions; genitourinary conditions; aging associated conditions; neurologic conditions; Th-2 dominant conditions etc.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the co-pending application

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teaches a method of treating autonomic nervous system abnormality comprising administering an agent such as a beta blocker in modulating at least a portion of parasympathetic/sympathetic activity.

The co-pending application does not teach administration of a non-beta blocking agent such as NSAID in a method of treating an autonomic nervous condition such as aging associated condition including hypertension.

Davies et al. teach the administration of ibuprofen, a non-steroidal anti-inflammatory drug along with an anti-hypertensive agent and a beta-blocker such as propranolol (see Abstract) to group of patients with hypertension.

It would have been obvious to one having ordinary skill in the art at the time of the invention to have added an NSAID along with a beta blocker such as propranolol in treating hypertension, an aging associated condition from the teachings of Davies et al. because the reference teaches that ibuprofen may be routinely administered to patients receiving propranolol without loss of control of the anti-hypertensive action of the drug.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1, 17, and 33 of co-pending application No. 11/592,027.

Claims 1, 21 of the instant application teaches a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an

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effective amount of at least one beta blocker to treat conditions that include genitourinary conditions e.g renal failure etc.

Claims 1, 17, 33 of the co-pending application teach a method of treating a subject for autonomic dysfunction such as renal associated condition such as renal failure comprising administering a pharmacological agent, such as beta blocker, metoprolol.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the co-pending application teaches a method of treating autonomic nervous system abnormality such as renal associated condition comprising administering an agent such as metoprolol, a beta blocker.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 11-28, 41, 62-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims are directed to a method of treating a subject for a condition caused by an autonomic nervous system abnormality, said method comprising providing a subject known to suffer from an autonomic nervous system abnormality administering to said subject an

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effective amount of a beta blocker and the abnormality is selected from conditions including neurodegenerative conditions; neuroinflammatory conditions; orthopedic inflammatory conditions; lymphoproliferative conditions; autoimmune conditions; inflammatory conditions; infectious diseases, pulmonary conditions; transplant-related conditions, gastrointestinal conditions; endocrine conditions; genitourinary conditions selected from the group of renal failure, hyperreninemia, hepatorenal syndrome and pulmonary renal syndrome; aging associated conditions; neurologic conditions; Th-2 dominant conditions; conditions that cause hypoxia; conditions that cause hypercarbia; conditions that cause hypercapnia; conditions that cause acidosis; conditions that cause academia, pediatric-related conditions; OB-GYN conditions, sudden death syndromes, fibrosis; post-operative recovery conditions; post-procedural recovery conditions; chronic pain; disorders of thermoregulation, cyclic vomiting syndrome and trauma. The specification describes the utility of administration of beta blockers in the subjects and further describes in detail the branches of the autonomous nervous system and the various disease conditions associated in modulating the autonomous nervous system, and the devices and systems for usage in such conditions. The specification in general teaches the dosage administration, routes, types of delivery, a list of beta blockers and non-beta blockers. The specification does not teach administration of a beta-blocker along with a non beta blocker to a subject known to suffer from an autonomic nervous system abnormality and treat such subjects for at least one of the conditions caused by autonomic nervous abnormalities listed in claim 1. The specification does not provide data or show any examples of actual administration of beta blockers along with a non-

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beta blocking agent in conditions arising from autonomic nervous system abnormality.

The scope of claim 23 is to use any beta blocker or any non-beta blocker agents in patients with one more conditions arising from autonomic nervous system abnormality.

The specification does not give any specific guidance to conditions resulting from abnormality of age associated autonomic nervous system regarding (1) criteria for the dosages for specific conditions (2) criteria for the counter indications in giving such beta blockers (3) criteria of dosage regimens for specific conditions e.g. when the dose needs to be administered, how many doses etc (4) criteria if patients suffer from multiple associated conditions. The patients can have multiple disease conditions and the therapy has to be patient specific and the conditions need to be monitored and it is not a trivial matter. Accordingly, the scope of the claims is broad. Also, the method claims comprise administering a non-beta blocker (claims 23 and 24) in addition to administration of a beta-blocker. The specification has not given any guidance (1) in regards with counter indications of all the non-beta blockers claimed (2) the dosage amount to be provided with respect to age related conditions to make sure there are no adverse effects or the side effects are to a minimal (3) precautions in administration of drugs for patients with more than one condition. Claim 72 is limited to beta-blocker propranolol and claim 84 is limited to an NSAID (a non beta blocker). However the scope of claim 1 treating conditions selected from the list and in addition at least one non-beta blocker is chosen from the list of claim 24 is large. Also, the scope of claim 78 is large with respect to the aging associated conditions that includes all types of cancer, heart conditions, diabetes, kidney conditions, neurodegenerative conditions etc.



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Accordingly, the conditions arising from such age associated conditions can be numerous. Also, the scope of claim 78 is very large with respect to the administration of at least one beta-blocker selected from the ones that is known and the ones to be discovered. The specification does not provide adequate description and there are no specific examples to provide support to the claims. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not provide support to the subject matter of administration of a beta blocker and a non-beta blocking agent to a subject to treat the said subject for at least one of the conditions listed in claim 1.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404

where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and, (8) the quantity of experimentation necessary.

Claims 1, 3, 4, 11-28, 41, 62-84 are rejected under 35 U.S.C. 112, first paragraph, because the prior art, while being enabling for a method of treating a subject

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for a condition caused by an autonomic nervous system abnormality comprising administering an effective amount of at least one beta blocker to conditions like asthma, hypertension, glaucoma, migraine, anxiety disorders does not reasonably provide enablement for treating all the diseases or disorders listed in claim 1 with all the beta blockers and in combination with all non-beta blocking agents listed in claim 24. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

***(1, 5) The nature of the invention and the breadth of the claims:***

The instant claims are directed to a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising administering an effective amount of at least one beta-blocker to said subject to treat said subject for at least one of: neurodegenerative conditions; neuroinflammatory conditions; orthopedic inflammatory conditions; lymphoproliferative conditions; autoimmune conditions; inflammatory conditions; infectious diseases, pulmonary conditions; transplant-related conditions, gastrointestinal conditions; endocrine conditions; genitourinary conditions selected from the group of renal failure, hyperreninemia, hepatorenal syndrome and pulmonary renal syndrome; aging associated conditions; neurologic conditions; Th-2 dominant conditions; conditions that cause hypoxia; conditions that cause hypercarbia; conditions that cause hypercapnia; conditions that cause acidosis; conditions that cause academia, pediatric-related conditions; OB-GYN conditions, sudden death syndromes, fibrosis; post-operative recovery conditions; post-procedural recovery conditions;

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chronic pain; disorders of thermoregulation, cyclic vomiting syndrome and trauma.

Claim 21 is limited to few beta blockers, claim 41 to few aging associated conditions.

The claims are not limited to any dosage amounts. Claim 72 is limited to beta-blocker propranolol and claim 84 is limited to an NSAID (a non beta blocker). Claims 1, 3, 4, 11-20, 22-28, 62, 63 are very broad with respect to the conditions, number of beta blockers, to the dosage amounts and to a number of non-beta blocking agents (listed in claim 24). The scope of claim 78 is large with respect to the aging associated conditions that include all types of cancer, heart conditions, diabetes, kidney conditions, neurodegenerative conditions etc. Accordingly, the scope of the conditions arising from such abnormalities is large. Also, the scope of claim 78 is very large with respect to the administration of at least one beta-blocker selected from the ones that is known and the ones to be discovered.

**(3) *The relative skill of those in the art:***

The relative skill of those in the pharmaceutical and medical arts is high, requiring advanced education and training.

**(2) *The state of the prior art:***

Stockley (Are Beta blockers safe?, BMJ, 298, 10 Jun 1989) teaches that two patients developed cardiac failure upon administration of nifedipine (a calcium channel blocker, one of the non beta blockers claimed in claim 24 of the instant application) along with propranolol or atenolol or alprenolol (p 1584, para 2). Chester et al. (Chest 79, 5, May 1981) teaches adverse effects of propranolol on airway function in nonasthmatic chronic obstructive lung disease patients (see Abstract). Houston (Cardiol

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Clin, 1986, Feb 4(1), 117-35) teaches that several antihypertensive drugs have an adverse effect on glucose tolerance that may partially or completely negate the beneficial effects of reducing blood pressure as it relates to the incidence of coronary heart disease and its complications and beta-blockers without intrinsic sympathomimetic activity have the greatest adverse effect on glucose intolerance. Liebermann et al. (Br J Obstet Gynaecol, 1978, 678-83, abstract) teaches that beta-adrenergic blockade is harmful to the hypoxic fetus, for these reasons the use of propranolol in hypertensive pregnancies complicated by placental insufficiency may be contraindicated unless there is no satisfactory alternative (See Abstract). Allen et al. teaches that there was an adverse effect of practolol, the occurrence of sinus bradycardia with or without an increase in the frequency of ventricular ectopic beats (See abstract). It has been well known in the prior art that beta blockers are useful in the treatment of angina, heart failure, high blood pressure, glaucoma and various disorders ([http://en.wikipedia.org/wiki/Beta\\_blocker](http://en.wikipedia.org/wiki/Beta_blocker)). Salpeter et al. (Cochrane Database of Systemic Reviews, 4, 2002) teach that beta blocker therapy has mortality benefits in patients with hypertension, heart failure, coronary artery disease as well as during the postoperative period (see Abstract). Also drugs that modulate adrenergic receptors such as beta blockers (e.g., metoprolol, atenolol) are known to cause inflammation to the joint (See Savola, BMJ, 287, 1983). In summary, the guidance from prior art is for the use of beta blockers in conditions like hypertension, heart failure, coronary artery disease as well as during the postoperative period, glaucoma etc, the adverse effects of certain beta blockers and the contraindications of beta blockers in combination with calcium channel blockers. The

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prior art or the specification does not teach that every single disease or disorder in the different classes of disorders (that are etiologically different) listed in claim 1 will be effectively treated by administration of the beta blockers (known and yet to be discovered) nor does the prior art or specification teach that every combination of beta blocker with a non-beta blocking agent can be used without interactions and be effective in the treatment.

**(4) *The predictability of the art:***

Despite the advance training of those in the art, the art is highly unpredictable. It is still not possible to predict the pharmacological activity or treatment efficacy of a compound based on the structure alone. It is also not possible to predict the efficacy of a given class of compounds for the treatment of a particular disease absent a mechanistic link between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Typically, in order to verify that a compound will be effective in treating a disease, the compounds must be either tested directly in a patient or in a model that has been established as being predictive of treatment efficacy. In order to predict whether a class of compounds would be effective in treating a disease, the etiology or pathophysiology of the disease must be uncovered, and there should be a nexus between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Absent experimental tests verifying the efficacy of a compound or a strong nexus between the known pharmacological activity of a class of agents and the etiology and/or pathophysiology of the condition, it is impossible to predict whether the compound or class of compounds (here beta

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blockers) would actually be effective for treating every single condition listed in claim 1. It is impossible to predict that every single beta blocker can be used in combination with every single non-beta blocker class of compounds listed in claim 24. It is impossible to predict that every single beta blocker used in a method of treatment of condition caused by an autonomic nervous system abnormality will be effective in the treatment of every single disorder or disease in the different classes of disorders (that are etiologically different) listed in claim 1. Stockley (Are Beta blockers safe?, BMJ, 298, 10 Jun 1989) teaches that two patients developed cardiac failure upon administration of nifedipine (a calcium channel blocker, one of the non beta blockers claimed in claim 24 of the instant application) along with propranolol or atenolol or alprenolol (p 1584, para 2). Hence it is highly unpredictable what the outcome would be due to the interaction of beta blockers with other drugs. Hence there is high unpredictability in the treatment of conditions arising from abnormal autonomic nervous disorders comprising administering a beta blocker with a non beta blocking agent. Chester et al. (Chest 79, 5, May 1981) teaches adverse effects of propranolol on airway function in nonasthmatic chronic obstructive lung disease patients (see Abstract). The unpredictability of the art is very high because there are hundreds of diseases listed in the claims of the instant application and a single disease or condition can be diagnosed via multiple biochemical pathways and treated via multiple biochemical pathways. The scope of enablement varies inversely with the degree of unpredictability of the factors involved, and physiological activity is generally considered to be unpredictable factor. There is a high degree of unpredictability involved in a method of treating a subject for a condition

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caused by an autonomic nervous system abnormality comprising administering an effective amount of at least one beta-blocker to said subject for all the diseases and disorders listed.

**(6, 7) *The amount of guidance presented and the presence of working examples:***

It has been established that, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839 166 USPQ 18, 24 (CCPA 1970). The specification describes the utility of administration of beta blockers in the subjects and further describes in detail the branches of the autonomous nervous system and the various disease conditions associated in modulating the autonomous nervous system, and the devices and systems for usage in such conditions. There are no working examples provided in the specification in a method of treating a subject for an autonomic nervous system abnormality comprising providing an effective amount of a beta blocker to a subject to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. The specification does not teach administration of a beta-blocker to a subject to treat such subjects for at least one of the conditions listed in claim 1. There is no guidance in the specification with respect to the treatment of conditions with high parasympathetic activity with normal sympathetic activity. The specification does not provide specific examples to provide support to the claims. Also, there is a high degree of unpredictability involved in combining a beta

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blocker with a non-beta blocking drug as there may be drug interactions and if there are any adverse effects such combination may not be workable. In summary, Applicant has provided little guidance beyond what was recognized in the art at the time of filing.

**(8) *The quantity of experimentation needed:***

In order to enable the instantly claimed methods commensurate with the entire scope, a large quantity of experimentation would be necessary. Disease states herein claimed do not flow from a single biochemical lesion, but form a range of physiological activities. The instant claimed maladies has no succinct etiological underpinnings, thus the recited conditions are not ameliorated by effecting a single biochemical lesion. That the instant maladies are not attributable to a single etiology, with the basis of the disease stated diffuse and multifaceted, the skilled artisan must test each compound against the envisioned biochemical lesion to determine the possible use of such compounds in the instant invention. With Applicants' guidance provided in the specification and what is known in the prior art the person of ordinary skill in the art would have to conduct these experiments administering beta blockers for every single condition associated with autonomic nervous system abnormalities listed in claim 1 and with combination of non-beta blockers listed in claim 24. Considering the unpredictability of the combination of compounds due to their drug interactions, this would be an arduous and daunting task. It would require undue experimentation to test each beta blocker for all the conditions associated in a method of treating the subjects with conditions associated with autonomic nervous system abnormality. It would require undue experimentation to test each beta blocker with every single non beta blocking



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agent listed in claim 24 for every condition associated with the listed autonomic nervous system abnormality. It would require undue experimentation to test all beta blockers for every condition listed in claim 1 to produce at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. Though the prior art has taught the use of certain beta blockers in conditions like heart disease, anxiety, hypertension etc it is not predictable from that data that every beta blocker would be useful in all the conditions associated with autonomic nervous system abnormalities listed namely, neurodegenerative conditions; neuroinflammatory conditions; orthopedic inflammatory conditions; lymphoproliferative conditions; autoimmune conditions; inflammatory conditions; infectious diseases, pulmonary conditions; transplant-related conditions, gastrointestinal conditions; endocrine conditions; genitourinary conditions selected from the group of renal failure, hyperreninemia, hepatorenal syndrome and pulmonary renal syndrome; aging associated conditions; neurologic conditions; Th-2 dominant conditions; conditions that cause hypoxia; conditions that cause hypercarbia; conditions that cause hypercapnia; conditions that cause acidosis; conditions that cause academia, pediatric-related conditions; OB-GYN conditions, sudden death syndromes, fibrosis; post-operative recovery conditions; post-procedural recovery conditions; chronic pain; disorders of thermoregulation, cyclic vomiting syndrome and trauma with the dosage amounts shown to be useful in specific conditions. Dosage depends on age, weight, pre-existing conditions, adverse effects, counter indications with drugs taken for other conditions etc. From the state of the prior art and from the guidance provided by

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the Applicants' it is not predictable that all the conditions listed in claim 1 when treated with beta blockers and a non-beta blocking agent would result in producing at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating a subject for a condition caused by an autonomic nervous system abnormality comprising administering an effective amount of at least one beta-blocker to said subject to treat said subject for at least one of the conditions listed in claim 1 and to produce at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. *Genetech*, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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Claims 1, 3, 4, 14, 16, 19-22, 28, 41, 62, 76-79 are rejected under 35 U.S.C. 102(b) as being anticipated by Gambardella et al. (Metabolism, 46, 3, March, 1999, p 291-297).

Gambardella et al. teach a method of treating a condition due to deficient parasympathetic activity associated with elevated basal metabolic rate in cancer patients by oral administration of propranolol (see Abstract, p 295, para 1, lines 1-8, p 296, para 4, 1-5). The reference teaches the autonomic nervous system dysfunction in cancer patients with elevated basal metabolic rate, there is an unbalanced sympathetic (SNS)/parasympathetic nervous system (PNS) ratio which may exist due to SNS over activity in cancer patients due to impaired PNS activity. The reference further teaches that beta-blocker such as propranolol administration may be useful to counteract the negative impact of the SNS on metabolic pathways (p 297, para 3 continued on 298). Hence the reference inherently teaches the sympathetic bias in at least a portion of autonomic nervous system, abnormality characterized by sympathetic bias, parasympathetic bias with an unbalanced SNS/PNS ratio with high SNS activity and low PNS activity. The administration of a beta blocker (propranolol) to a cancer patient in a method of treating a condition caused by an autonomic nervous system abnormality meets the structural limitation of the claim. Accordingly, the reference inherently teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

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Claims 1, 3, 4, 11-12, 15, 17, 21, 28, 41, 62, 72 are rejected under 35

U.S.C. 102(b) as being anticipated by Brevetti et al. (Brief communications, Nov 1981, p 938-941).

Brevetti et al. teach an intravenous and oral administration of propranolol for the treatment of Shy-Drager syndrome, a severe degeneration of the autonomic nervous system. The reference further teaches that orthostatic hypotension a condition of Shy-Drager syndrome is mainly dependent on peripheral vasodilation without the normal response of postural vasoconstriction and may be a consequence of an imbalance of alpha and beta adrenoreceptor activity in peripheral nervous system and that beta-blockade may provide an effective means of treating orthostatic hypotension in patients with Shy-Drager syndrome (p 940 para 2, lines 1-5, continued on page 941). The reference teaches a sympathetic bias and a parasympathetic bias in at least a portion of said autonomic nervous system. In summary, Brevetti et al. teaches administration of a beta blocker such as propranolol in patients suffering from Shy-Drager syndrome an autonomic nervous system abnormality. The administration of a beta blocker (propranolol) to a Shy-Drager syndrome patient in a method of treating autonomic nervous system abnormality meets the structural limitation of the claim. Accordingly, the reference inherently teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Claims 1, 21, 23-25, 28, 69, 74-76 are rejected under 35 U.S.C. 102(b) as being anticipated by Davies et al. (The J of Intl Med Research, 1988, 16, 173-181).

Davies et al. teach the administration of ibuprofen, a non-steroidal anti-inflammatory drug along with an anti-hypertensive agent and a beta-blocker such as propranolol (see Abstract) to group of patients with hypertension. It is inherent that hypertension, an age-associated condition is common in elderly patients and parasympathetic nerves influence cerebral blood flow during hypertension. In summary, Davies et al. teaches administration of a beta blocker such as propranolol in patients suffering from hypertension, an age associated condition, also an autonomic nervous system abnormality. Davies et al. in p 174, in Patients and Methods section teaches measuring blood pressure in patients and further teach that patients showing a clinically significant rise in blood pressure ( $>5$  mm Hg) rise in diastolic blood pressure were eligible to continue. Accordingly, the reference teaches identification of a subject known to suffer from an autonomic nervous system disorder. The administration of a beta blocker (propranolol) to patient with hypertension in a method of treating autonomic nervous system abnormality meets the structural limitation of the claim. Accordingly, the reference inherently teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject.

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Claims 1, 16, 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Bugiardini et al. (Am J Cardiol, 1989, Feb 1, 63, 5, 286-90) as evidenced by Guilli et al. (Cardiovascular Research, 2001, 208-216).

Bugiardini et al. teach administration of propranolol to patients with X syndrome and further teach that the average number of ischemic episodes per 24 hours was significantly reduced during propranolol therapy compared with placebo (see abstract).

Guilli et al. teach that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity (see Abstract).

Bugiardini's teachings anticipate the claim of treating an autonomic nervous condition comprising administering beta propranolol because the reference teaches administration of a beta-blocker propranolol to patients with X-syndrome and Guilli et al. teach that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity. The administration of a beta blocker (propranolol) to patient with X-syndrome in a method of treating autonomic nervous system abnormality condition meets the structural limitation of the claim. Accordingly, the reference inherently teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject.

Claims 1, 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Shimizu et al. (J of the Amer. College of Cardiology, 39, 12, June 2002) as evidenced by Morita et al. (Jpn Circ J 1996, Oct 60(10), 742-8).

Shimizu et al. in the abstract teaches the administration of propranolol to patients with LQT1 or LQT2 syndrome under normal sympathetic tone or during sympathetic stimulation.

Morita in the abstract teaches that The pathogenesis of LQTS and the induction of TdP have been thought to be closely related to autonomic nervous abnormalities and LQTS patients with TdP had lower abnormal sympathetic nervous activity than those without TdP

Shimizu et al's teachings anticipate the claim of treating an autonomic nervous abnormality condition because the reference teaches administration of a beta-blocker propranolol to patients with LQT-syndrome under normal tone or during sympathetic stimulation conditions and Morita et al. teaches that LQTS patients have autonomic nervous system abnormalities. Accordingly, the administration of a beta blocker (propranolol) to patient with LQT-syndrome meets the structural limitation of the claim of administering a beta blocker to a subject with autonomic nervous system abnormality. Accordingly, the reference inherently teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 63, 70, 71, 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lampert et al. (The Am J of Cardiology, 91, 2, Jan 2003) and Gambardella et al. (Metabolism, 46, 3, March, 1999, p 291-297) in view of Idekar et al. (U.S. 5,522,854).

Lampert et al. teaches propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction patients (see Abstract, p 140, Discussion, para 1). Thus from the teachings of Gambardella et al. and Lampert et al. it is evident that parasympathetic activity is increased after propranolol administration with heart conditions. Lampert et al. teach administration of 180 or 240 mg/day of propranolol (See Methods).

Gambardella et al. teachings discussed as above.

It would have been obvious to one of ordinary skill in the art at the time of the invention that administration of a beta blocker such as propranolol increases the parasympathetic activity because of the teachings of Lampert et al. Lampert et al. teach that propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction patients. Hence by administration of same drug (as claimed), propranolol to patients would obviously have the same pharmacological effects such as increase in parasympathetic activity. The reference does not explicitly teach that administration of beta blockers produce parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a



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healthy 25 year old human subject. However, Lampert et al. teach administration of propranolol 180 or 240 mg/day. The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence administration of the same compound with the suggested dosage amount (as in the specification of the instant application) to a subject with an autonomic nervous system abnormality condition would produce the same pharmacological effects of producing parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject.

The references do not teach determining the parasympathetic/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system.

Ideker et al. teaches that a preferred way to measure the ratio of sympathetic to parasympathetic nerve activity is to measure heart rate variability, as will be appreciated by those skilled in the art, with a decrease in heart rate variability indicating an increased risk of the onset of arrhythmia (col.3, lines 49-52).

It would have been obvious to one having ordinary skill in the art at the time of the invention to have measured the parasympathetic/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system from the teachings of Idekar et al. because the reference teaches a method to measure the ratio of sympathetic to parasympathetic nerve activity is to measure heart rate variability. One having ordinary skilled in the art at the time of the invention would have been motivated to determine the

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parasympathetic/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system is to use the ratio as an indicator to whether there is a decrease in heart rate variability that is associated with an increased risk of the onset of arrhythmia. It would have been obvious to one having ordinary skill in the art to have used a beta blocker in response to the determined parasympathetic/sympathetic activity ratio because Lampert et al. teach the therapeutic benefits of administration of a beta blocker propranolol in patients with myocardial infarctions, an autonomic nervous system abnormality.

Claims 64-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gambardella et al. (Metabolism, 46, 3, March, 1999, p 291-297) as applied to claims 1, 3, 4, 14, 16, 19-22, 28, 41, 62, 76-79 above and in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003).

Gambardella et al. teachings discussed as above.

The reference does not explicitly teach employing control feedback loop.

Mann et al. teaches therapeutic treatment for cardiac diseases comprising sensors. The reference further teaches that patients can be titrated to higher or more appropriate beta-blocker dose levels with potentially increased survival benefits (see abstract, para 380) based on the signals.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann et al. One having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop

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in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions. It would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensors in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol. The dosage administration is clearly a dose effective parameter that a person of ordinary skill in the art would routinely optimize. It would have been obvious to modulate the autonomic nervous system administering two different beta blocker protocols from the prior art teachings of Gamberdella, Mann et al, (para 321). From the teachings of Mann it would have been obvious to one of ordinary skill in the art to administer different doses or administer same or different beta blocker protocols in treating the disease conditions due to the modulation of autonomic nervous system from the output of the sensor signals and to produce parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject.

Claims 80 and 81 are rejected as being unpatentable over Gambardella et al. (Metabolism, 46, 3, March, 1999, p 291-297) as applied to claims 1, 3, 4, 14, 16, 19-22, 28, 41, 62, 76-79 above and in view of Nelson et al. (Support Care Cancer 2002, 10:523-528).

Gambardella et al. teachings discussed as above.

The reference do not teach the determination of parasympathetic and sympathetic activity ratio in at least a portion of said subject's autonomic nervous system (ANS).

Nelson et al. teaches the autonomic nervous system abnormality in cancer patients. The reference further teaches the methods of measuring the parasympathetic and sympathetic functions of ANS in cancer patients.

It would have been obvious to one having ordinary skill in the art at the time of the invention to have used the method of Nelson to measure the parasympathetic and sympathetic activities to evaluate the conditions or symptoms associated with ANS abnormalities (such as cancer). One having ordinary skill in the art would have been motivated to determine of parasympathetic and sympathetic activity ratio in at least a portion of said subject's autonomic nervous system to evaluate the ANS in advanced cancer. It would have been obvious to one having ordinary skill in the art at the time of the invention to have administered an effective amount of at least one beta blocker based on the ratio of parasympathetic and sympathetic ratio to modulate the ANS to provide effective therapy to cancer patients.

Claims 82-84 are rejected as being unpatentable over Gambardella et al. (Metabolism, 46, 3, March, 1999, p 291-297) as applied to claims 1, 3, 4, 14, 16, 19-22, 28, 41, 62, 76-79 above and in view of Jatoi et al. (<http://www.psychiatrictimes.com/display/article/10165/86028?pageNumber=1>).

Gambardella et al. teachings discussed as above.

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The reference do not teach administration of an NSAID, a non beta-blocker in treatment of a condition (weight loss) caused by an autonomic nervous system abnormality (cancer, an aging associated condition with loss of parasympathetic function).

Jatoi et al. teaches that non steroidal anti-inflammatory agents such as ibuprofen can be used to halt the wasting process associated with the cancer associated weight loss (see abstract, p8, p 9- Ibuprofen).

It would have been obvious to one having ordinary skill in the art at the time of the invention to have administered an NSAID in a method of treating a condition such as weight loss caused by autonomic nervous system abnormality, cancer because of the teachings of Jatoi et al. One having ordinary skill in the art at the time of the invention would have been motivated to administer an NSAID drug such as ibuprofen along with a beta blocker such as propranolol to cancer patients in an attempt to halt the wasting process associated with the cancer associated weight loss. The references do not explicitly teach that the propranolol and NSAID are administered in unit dosage forms. However it would have been obvious to one having ordinary skill in the art at the time of the invention that amount or dosage of drugs is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. It is well within the skilled medical professional to determine suitable dosing regimens in order to provide effective therapy.

***Response to Arguments***

*1) 112(1) Written Description rejection:*

Applicants' argue that in view of the support in the literature for the discovery that autonomic nervous system disturbances underlie many different diseases, and because the pharmacologic agents used in the subject methods are well-known to affect the autonomic nervous system, there is no evidence that use of the claimed pharmacological agents to treat the claimed diseases would not be successful. One of skill in the art would not need specific examples and doses in order to provide adequate written description of this approach of modulating autonomic function to treat multiple diseases.

In response, the examiner does not dispute the fact that various beta blockers or non-beta blocking agents and the dosages are known in the literature. However, the claims of the instant invention are towards treating autonomic nervous system abnormality with at least one beta blockers and additionally at least one non beta blocking agent. The claims are very broad with respect to all the beta blocking agents, non beta blocking agents and to the unrelated disorders that encompasses a vast array of neurodegenerative conditions, neuroinflammatory conditions; orthopedic inflammatory conditions; lymphoproliferative conditions; autoimmune conditions; inflammatory conditions; infectious diseases, pulmonary conditions; transplant-related conditions, gastrointestinal conditions; endocrine conditions; genitourinary conditions selected from the group of renal failure, hyperreninemia, hepatorenal syndrome and pulmonary renal syndrome; aging associated conditions; neurologic conditions; Th-2

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dominant conditions; conditions that cause hypoxia; conditions that cause hypercarbia; conditions that cause hypercapnia; conditions that cause acidosis; conditions that cause academia, pediatric-related conditions; OB-GYN conditions, sudden death syndromes, fibrosis; post-operative recovery conditions; post-procedural recovery conditions; chronic pain; disorders of thermoregulation, cyclic vomiting syndrome and trauma. The examiner is aware that the various disease states encompassed by the claims can be identified and treated. However, while it is known to identify different conditions and their treatments in the art, it is a totally different issue when one of skilled in the art attempts to treat all these seemingly art-recognized to be unrelated disorders with a single agent (beta blocker). Such concept is not known. And as admitted by the applicant this is the novelty of the instant invention. Since the concept is novel, the guidance required to enable one of skilled in the art would be significantly more. However, in the instant case, there is no sufficient guidance provided in the instant case of how different beta blockers would be used alone or with different beta blocking agents to treating all the conditions listed. The only nexus, according to the instant specification, for linking all the disorders encompassed by the claims is the parasympathetic/sympathetic activity, an autonomic nervous system abnormality. The specification describes the utility of administration of beta blockers in the subjects and further describes in detail the branches of the autonomous nervous system and the various disease conditions associated in modulating the autonomous nervous system, and the devices and systems for usage in such conditions. However, the examiner notes that there is no working example disclosed in the instant specification. It is not

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known in the art that all of the beta blockers and the entire non beta blocking agents disclosed in the instant specification would affect the autonomic nervous systems. Moreover, drugs that modulate adrenergic receptors such as beta blockers (e.g., metoprolol, atenolol) are known to cause inflammation to the joint (See Savola, BMJ, 287, 1983). The specification has not given any guidance (1) in regards with counter indications of all the non-beta blockers claimed when administered along with a beta blocker (2) the dosage amount to be provided with respect to age related conditions to make sure there are no adverse effects or the side effects are to a minimal (3) precautions in administration of drugs for patients with more than one condition. Absent evidence to the contrary demonstrating a working invention, the instant claims are considered properly rejected under 35 USC 112, first paragraph.

*2) 112(1) Enablement rejection*

Applicants' argue that "The inventors of the subject invention have formulated novel pharmacologic strategies to treat conditions including disease conditions by modulating autonomic function as the basis of therapy. Extensive support for this theory including multiple specific examples of diseases that can be treated along with references can be found in the specification, for example on p. 4, line 9 to p. 5, line 26, and p. 59, line 11 to p. 67, line 29". Applicants' further argue that treatment with beta blocking agents is well known in the art and directions for treatment can be found in the literature.

In response, the claims encompass an immense and diverse class of conditions that arise from immense and diverse class of autonomic nervous system abnormality



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that has been claimed. The specification describes the utility of administration of beta blockers in the subjects and further describes in detail the branches of the autonomous nervous system and the various disease conditions associated in modulating the autonomous nervous system, and the devices and systems for usage in such conditions and in general teaches the dosage administration, routes, types of delivery, examples of beta blockers and non-beta blockers. The specification however does not provide any other guidance or provide working examples for even one of the laundry list of disease conditions listed in claim 1. The claims encompass a vast array of disorders resulting from autonomic nervous system abnormality. The examiner notes that apparently, the applicant does not realize the broadness of the instant claims. The claims are so broad that they encompass at least one beta blocker and an addition of at least one non beta blocking agent in a method to treat all diseases listed. Furthermore, these different diseases encompass vastly diverse disorders that are well-recognized in the art having different etiologies. There is no working example disclosed in the instant specification that one single agent could treat all conditions arising from autonomic nervous system abnormality. Even *arguendo*, the examiner clearly demonstrates that the full scope of the invention is not enabled because beta-blockers can cause joint inflammation according to Savola. Moreover, providing or listing all of the compounds do not mean providing "blaze marks", direction, and/or guidance to one of skilled in the art so that one of skilled in the art can practice the full scope of the invention without undue experimentation. The examiner further notes that although the compounds are individually well-known in the art, they are not well-known to be useful in treating the

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disorders claimed. The examiner does not dispute the fact that the various disease states encompassed by the claims can be identified and treated. However, while it is known to identify different conditions and their treatments in the art, it is a totally different issue when one of skilled in the art attempts to treat all these seemingly art-recognized to be unrelated disorders with a single agent. Such concept is not known. And as admitted by the applicant this is the novelty of the instant invention. Since the concept is novel, the guidance required to enable one of skilled in the art would be significantly more. However, in the instant case, there is no sufficient guidance provided in the instant case. The only nexus, according to the instant specification, for linking all the disorders encompassed by the claims is the parasympathetic/sympathetic activity. The examiner notes that there is no working example disclosed in the instant specification. Applicants have not provided any evidence from the prior art or with working examples that the listed beta-blockers in combination with a non beta blocker would have been reasonably expected to treat the range of conditions arising from the diseases listed. It is not known in the art that beta blocking agents and all of the non-beta blocking agents disclosed in the instant specification would affect the autonomic nervous systems. Moreover, drugs that modulate adrenergic receptors such as beta blockers (e.g., metoprolol, atenolol) are known to cause inflammation to the joint (See Savola). Although the method of the instant invention is not to discover specific compounds, it is to use these compounds to treat seemingly unrelated disorders. Taking the broadness of the claims, the lack of guidance in the specification, the state of the art, the predictability of the field, and the absence of the working example together,

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one of skilled in the art would have to perform undue experimentation to practice the full scope of the claims. The state of the art is that it is not known to use a single agent to treat all unrelated disorders listed in the claims. Absent evidence to the contrary demonstrating a working invention, the instant claims are considered properly rejected under 35 USC 112, first paragraph. *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1005 (Fed. Cir. 1997) states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and [p]agent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable". It will be an undue experimentation to enable use for the full scope of the instantly claimed invention. Accordingly, the claims are considered properly rejected under 35 USC 112, first paragraph.

(3) ODP rejections:

(1) Rejection over co-pending application No. 11/060,643: Applicants' argue that "the current claims include adding at least one beta blocker and parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system is analogous to the parasympathetic activity-sympathetic activity ratio observed in a healthy 25 year old human subject. This is in contrast to the claims in the co-pending application, which are directed to increasing the parasympathetic activity/sympathetic activity ratio in a manner effective to treat a subject for a condition". In response, by modulating the parasympathetic and sympathetic activity in autonomic nervous conditions comprising stimulating a portion with at least one electrode and applying electrical energy the disease is treated. Upon using the same conditions

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(electrical stimulation) as in the co-pending application and treating the condition, it would have been obvious to one having ordinary skill in the art at the time of the invention that the parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. Though the co-pending application do not teach a beta blocker, it is well known in the art (Bugiardini et al.) that propranolol a beta blocker has been used in treating patients with X syndrome (patients with transient myocardial ischemia without evidence of coronary atherosclerosis or vasospasm). Guilli et al. teach that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity (see Abstract). Hence from Bugiardini's teachings it can be evidenced that parasympathetic and sympathetic activity is modulated. It would have been obvious to one having ordinary skill in the art at the time of the invention to have used a beta blocker in addition to the electrical stimulation in treating an autonomic nervous condition in expectation of achieving better therapeutic benefits. Accordingly, the rejection is maintained.

(2) Rejection over co-pending U.S. Application No. 10/962,190: Applicants' argue that co-pending application is directed to using one aldosterone antagonist and the current claims are directed to administration of a beta blocker. In response the co-pending application teaches comprising administering an aldosterone antagonist and a non-aldosterone antagonist (Selected from beta blockers, angiotensin receptor blockers etc). The claims of the instant application has a comprising language and teaches administration of a beta blocker and do not exclude addition of an aldosterone

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antagonist. As stated above, by modulating the parasympathetic and sympathetic activity in autonomic nervous conditions comprising administering an aldosterone antagonist and a non-aldosterone antagonist the autonomic nervous condition is treated. Upon using the same beta blockers as in the co-pending application and treating the condition, it would have been obvious to one having ordinary skill in the art at the time of the invention that the parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. Accordingly, the rejection is maintained.

(3) Rejection over co-pending U.S. Application No. 11/592,027: Applicants' argue that co-pending application is directed to a method of treating renal associated condition. In response, the instant application is toward treating an autonomic nervous abnormality including genitourinary conditions e.g renal failure etc comprising administering a beta blocker. The co-pending application teaches method of treating renal associated condition comprising administering a pharmacological agent such as metoprolol, a beta blocker. Hence administration of the same pharmacological agent in treating a renal associated condition obviously teaches a method of treating an autonomic nervous condition, a renal condition such as renal failure comprising administering a beta blocker such as metoprolol. Upon using the same beta blockers as in the co-pending application and treating the condition, it would have been obvious to one having ordinary skill in the art at the time of the invention that the parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic

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nervous system is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. Accordingly, the rejection is maintained.

(4) 102 rejections:

(1) Gambardella et al. (Metabolism, 46, 3, March, 1999, p 291-297)

Applicants' argue that Gambardella et al. fails to teach the element of producing a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject as the goal of the study is towards weight loss. In response, the reference teach a method of treating a condition due to deficient parasympathetic activity associated with elevated basal metabolic rate in cancer patients by oral administration of propranolol. The autonomic nervous system abnormality is cancer (an age associated condition) and the weight loss is the condition associated with the abnormality. Hence treating weight loss associated with cancer, Gambardella et al. teaches treating a condition caused by autonomic nervous system abnormality. The reference teaches administration of 40 mg twice daily (80 mg/day) of propranolol in cancer patients, which falls in the range of the suggested dosage by the Applicants (80 mgs. to about 320 mgs/day Specification para 0091). Accordingly, administration of the same drug in the same dosage range as claimed by the Applicants used in a method of treating weight loss in cancer patients inherently teaches attaining the autonomic nervous system that is analogous to the

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parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. Accordingly, the rejection is maintained.

(2) Brevetti et al. (Brief communications, Nov 1981, p 938-941).

Applicants' argue that Brevetti does not anticipate the claimed invention and does not specifically disclose treating a condition by administering an effective amount of a beta blocker to produce para sympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

In response, Brevetti teaches orthostatic hypotension is among the most discomforting conditions in the first stage of Shy-Drager (SD) syndrome. The prior art teaches that administration of intravenous propranolol (10 mg) followed by oral propranolol (40 mg) has been shown to be useful in treating orthostatic hypotension symptoms in SD syndrome. In summary, Brevetti et al. teaches administration of a beta blocker such as propranolol in patients suffering from Shy-Drager syndrome an autonomic nervous system abnormality. Upon using the same beta blocker, propranolol as claimed by the Applicants' and treating the symptom of the condition, it would have been obvious to one having ordinary skill in the art at the time of the invention that the condition is treated and parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. Accordingly, the rejection is maintained.

(3) Davies et al. (The J of Intl Med Research, 1988, 16, 173-181).

Applicants' argue that Davies discloses that ibuprofen does not substantially affect treatment of hypertension in patients on beta-blockers or thiazides, however there is no discussion in Davies of the autonomic nervous system. Applicants' further argue that Davies do not anticipate the instantly claimed invention.

In response, Davies teaches administration of ibuprofen (NSAID) with propranolol to patients with hypertension (it is well known that hypertension is an aging associated condition). The reference teaches that ibuprofen may be routinely administered to patients receiving propranolol without loss of control of the anti-hypertensive action of the drug. Thus a patient who has a hypertensive condition with painful disorders of muscles and joints can take ibuprofen while taking propranolol according to Davies. Davies study teaches administration of 40-240 mg/day of propranolol which falls in the range of the suggested dosage by the Applicants (80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses, Specification para 0091). Accordingly, administration of the same drug in the same dosage range as claimed by the Applicants used in a method of treating hypertension (an aging associated condition) inherently teaches attaining the autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. Accordingly, the rejection is maintained.

(4) Bugiardini et al. (Am J Cardiol, 1989, Feb 1, 63, 5, 286-90)

Applicants' argue that Bugiardini does not disclose treating a condition by administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's



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autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

In response, Bugiardini teaches that propranolol a beta blocker has been used in treating patients with X syndrome (patients with transient myocardial ischemia without evidence of coronary atherosclerosis or vasospasm). Guilli et al. teach that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity (see Abstract). Hence from Bugiardini's teachings it can be evidenced that parasympathetic and sympathetic activity is modulated. The reference teaches providing propranolol in a dose ranging from 120-160 mg/day, which falls in the range of the suggested dosage by the Applicants (80 mgs. to about 320 mgs/day Specification para 0091). Accordingly, administration of the same drug in the same dosage range as claimed by the Applicants used in a method of treating angina (an aging associated condition) inherently teaches attaining the autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. Accordingly, the rejection is maintained.

(5) Shimizu et al. (J of the Amer. College of Cardiology, 39, 12, June 2002)

Applicants' argue that Shimzu does not teach the claimed elements.

In response, Shimzu teaches the administration of propranolol to patients with LQT1 or LQT2 syndrome under normal sympathetic tone or during sympathetic stimulation. Shimzu teaches administration of oral propranolol (0.5-2.0 mg/kg /day). Accordingly, the reference teaches administration of propranolol in the range of 30-120 mg for a 60 kg weight patient, which falls in the range of the suggested dosage by the

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Applicants (80 mgs. to about 320 mgs/day Specification para 0091). Accordingly, administration of the same drug in the same dosage range as claimed by the Applicants used in a method of treating long QT syndrome (is a rare inborn heart condition, an aging associated condition) inherently teaches attaining the autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. Accordingly, the rejection is maintained.

(5) 103(a) rejections:

(1) Lampert et al. (The Am J of Cardiology, 91, 2, Jan 2003), Idekar et al. (U.S. 5,522,854).

Applicants argue that Lampert does not teach the element of providing a subject known to suffer from an autonomic nervous system abnormality. Further, there is no disclosure in Lampert that teaches or suggest the claimed elements.

In response, Lampert teaches administration of propranolol (180-240 mg/day) to patients (between age of 30-69 and mean age of 54) with myocardial infarction (heart attack, aging associated condition). Applicants suggest administration of 80 mgs. to about 320 mgs/day Specification para 0091 in treating autonomic nervous conditions. Administration of the same compound with the suggested dosage amount (as in the specification of the instant application) to a subject with an autonomic nervous system abnormality condition would produce the same pharmacological effects of producing parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity

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/sympathetic activity ratio observed in a healthy 25 year old human subject. Accordingly, the rejection is maintained.

Applicants' argue that the Office has not articulated a sufficient reason why one of skill in the art would look to a ratio for assessing risk of arrhythmia as in Ideker in using the method of Lampert.

In response, Ideker et al. teaches that a preferred way to measure the ratio of sympathetic to parasympathetic nerve activity is to measure heart rate variability. It is known in the art that heart rate variability (HRV) measurements provide a noninvasive method to assess cardiac autonomic function in humans. It is known that the heart rate variability is associated with myocardial infarction and sinus arrhythmia is associated with myocardial infarction (Wolf, Med J Aust 1978, 12, 2, 52-3). Hence by using Ideker et al it would have been obvious to a person of ordinary skill in the art that the ratio of sympathetic to parasympathetic nerve activity in an autonomic condition such as myocardial infarction condition in Lampert's studies can be measured.

### **Conclusion**

No claims are allowed.

Applicants' amendments necessitated the new and modified rejections presented in this office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627